REMARKS

I. STATUS OF THE CLAIMS

After entry of the present amendments, claims 1, 7, 9, 17-30, 44-46, 48, 49, 52, 54, 56, 59, 63, 66, 77, 79, 100, 104, 111, 119, 121, 122 and 124-130 will be pending in the present application. Claims 2, 112-118, 120 and 123 have been canceled, without prejudice or disclaimer. Claims 1, 7, 9, 17-30, 44-46, 48, 49, 52, 54, 56, 59, 63, 66, 77, 79, 100, 104, 111, 119, 121 and 122 have been amended. Claims 124-130 have been added. Support for the new and amended claims can be found throughout the specification and claims as filed, including, for example, paragraphs [0810], [0822], [0861], and [1064]-[1072] of the published application. No new matter has been added. No claim amendment should be construed as an acquiescence in any ground of rejection. Claims have been amended without prejudice to pursuing the canceled subject matter in one or more related applications.

II. ELECTION OF SPECIES

The examiner has acknowledged applicants' election of species and claims 22-26, 28-30, 44-46, 48, 49, 52, 56, 59, 77, 100, 104, 122, 128 and 129 have been withdrawn. It is applicants' understanding that the examiner will proceed to examine withdrawn claims if the pending claims are found to be allowable over the prior art.

III. AMENDMENT TO THE SPECIFICATION

As suggested by the examiner, applicants have amended the abstract to describe the nature of, and exemplary uses for, the claimed conjugates. The specification has also been amended such that the trademark "CHROMATOTRON®" is capitalized and accompanied by generic terminology, as suggested by the examiner. The paragraph on page 180, lines 34-37 of the specification has been replaced. Support for the amendment can be found at p. 166, line 33 to p. 167, line 7 of the priority application, Serial No. 60/400,403. The text on p. 181 of the specification that reads "not furnished upon filing" has been deleted.

IV. THE CLAIMS ARE PATENTABLE UNDER 35 U.S.C. § 112 FIRST PARAGRAPH

WRITTEN DESCRIPTION

Claims 1, 2, 7, 9, 17-21, 27, 54, 63, 66, 79, 111-121 and 123 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking adequate written description for pharmaceutically acceptable solvates. Applicants respectfully disagree. However, without acquiescing to the rejection and solely to expedite prosecution of the instant case, applicants have amended claims 1, 2, 7, 9, 17-21, 27, 54, 63, 66, 79, 111-121 and 123 to delete pharmaceutically acceptable solvates, while maintaining coverage of "pharmaceutically acceptable salt[s]" (including pharmaceutically acceptable salts in solution).

Accordingly, applicants request withdrawal of the rejections under § 112, first paragraph for lack of written description.

ENABLEMENT

Solvates

Claims 1, 2, 7, 9, 17-21, 27, 54, 63, 66, 79, 111-121 and 123 stand rejected under 35 U. S.C. § 112, first paragraph, for allegedly failing to enable a person skilled in the art to make and/or use pharmaceutically acceptable solvates. Applicants respectfully disagree. However, without acquiescing to the rejection and solely to expedite prosecution of the instant case, applicants have amended claims 1, 2, 7, 9, 17-21, 27, 54, 63, 66, 79, 111-121 and 123 to delete pharmaceutically acceptable solvates, while maintaining coverage of "pharmaceutically acceptable salt[s]" (including pharmaceutically acceptable salts in solution). Applicants therefore request withdrawal of the rejections under § 112, first paragraph for lack of enablement with respect to pharmaceutically acceptable solvates.

Scope of Enablement

Claims 111-119 stand rejected under 35 U. S.C. § 112, first paragraph, for allegedly failing to enable a person skilled in the art to make and/or use the invention commensurate in scope with the claims. According to the Office Action, it would require undue experimentation to practice the invention of claims 111-119 because the "level of unpredictability in treating cancer, autoimmune disorders and infectious diseases is high and the instant specification provides very little guidance." Office Action, p. 11. Without

acquiescing to the rejections and solely to expedite prosecution of commercially relevant subject matter, applicants have herein canceled claims 112-118 directed to therapeutic methods. Claim 119 is directed to compounds, but the rejection for lack of enablement refers to pharmaceutical compositions (e.g., claim 111) and methods of treatment (e.g., claims 112-118), not compounds. The enablement rejection is therefore not applicable to claim 119 and new claims 126-127. Accordingly, applicants request that the rejection of claim 119 for lack of enablement be withdrawn. Applicants traverse the rejection of claim 111.

Questions of enablement are evaluated against the *claimed* subject matter. M.P.E.P. § 2164.08. Where a claimed composition is not limited by an intended use or effect, disclosure of any manner of making and using the composition is sufficient to preclude a rejection for non-enablement. *See Id.* at § 2164.01(c). Notably, claim 111 is a product claim which is not limited by an intended use or effect. Thus, the disclosure of any manner of making and using the claimed compositions is sufficient for enablement of claim 111.

A disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing the claimed subject matter ***must*** be taken as in compliance with the enablement requirement ***unless*** there is reason to doubt the objective truth of the statements contained therein. *In re Marzocchi,* 439 F.2d 220, 223 (CCPA 1971); M.P.E.P. § 2164.04. Thus, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for a claimed invention. *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993).

Viewed in this context, there is simply no reason to doubt the enablement of the claimed compositions. The specification provides ample guidance on how to make and use the compositions of claim 111. For example, schemes, methods and protocols for making and isolating compounds of claim 111 are described in paragraphs [0969]-[1063] and Examples 1-40 of the published application, and carriers, vehicles, excipients, formulations, and the like for pharmaceutical compositions are described in paragraphs [1064]-[1072] and [1085]-[1094] of the published application. Exemplary uses, including, e.g., treating cancer, and routes of administration, dosage ranges, and the like are described in paragraphs [1073]-[1084] and [1095]-[1125] of the published application, and Examples 41-50 disclose data showing anticancer activity *in vitro* and *in vivo*. In light of the guidance in the specification

and high level of skill in the pharmaceutical art, a skilled artisan could have readily made the claimed compositions and administered them to subjects without undue experimentation. Accordingly, applicants request that the rejection of claim 111 for lack of enablement be withdrawn.

The examiner's assertion of non-enablement is based on an analysis under *In re Wands*, relying primarily on evidence relating to the state of the prior art and its degree of predictability, the amount of direction or guidance presented, and the presence or absence of working examples. These factors are addressed in turn below.

The State of the Prior Art and its Predictability or Unpredictability

The Office Action alleges that "while drugs may be effective *in vitro* and in mice, they are not necessarily effective in humans" since "model systems are not predictive of *in vivo* activity." Office Action, p. 8. Specifically, several articles are cited alleging that "petri dish cancer ... [has] characteristics profoundly different from human disease," that "xenograft models in mice don't behave like naturally occurring tumors in humans," and that "other systems such as clonogenic assays ... can't always predict how a tumor will respond to a drug in an animal." *Id.*

The examiner mistakenly relies upon the cited articles to support an allegation that those skilled in the art would not believe that the claimed compounds can be used for the treatment of cancer. It is, however, well known that animal studies are widely used and generally accepted by the U.S. Food and Drug Administration to provide support for clinical trials in the United States. By asserting the cited articles as evidence of the state of the art and as evidence of non-enablement of the claims, the examiner appears to be requiring a higher standard of predictability than is required by the United States Patent Laws. The United States Patent Laws simply requires the applicant to demonstrate a reasonable correlation between a particular activity and an asserted use. M.P.E.P. § 2107.03. Applicants have demonstrated such a correlation, see, for example, the data provided in examples 41-50 of the specification. It is well established that such data is sufficient to satisfy the utility prong of U.S.C. § 112. *In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1995); MPEP § 2107.03.

The Amount of Direction or Guidance Presented and the Presence or Absence of Working Examples

The Office Action alleges that the "the specification lists *in vitro* cytotoxic assay methods," but "fails to provide any data obtained using the compounds of the claimed invention." Office Action, p. 9. To the contrary, examples 41-50 of the specification describe data showing cytotoxic activity for a number of representative compounds. The Office Action also alleges that "one cannot readily conclude whether the claimed compounds will behave the same as the native biologically active compound [since] the claimed molecules contain large moieties that can effect biological activities." *Id.* In referring to the "large moieties," the examiner implies that the data is limited to compounds comprising only the Drug portion of the conjugates. To the contrary, data is provided for both active drugs and drug conjugates comprising a Drug linked to a Ligand, including, for example, compounds 64-67, 91 and 92.

The Office Action also alleges that the specification fails to provide guidance on whether the claimed compounds "can be used to treat the innumerable cancers encompassed by the claims," and fails to provide "working examples of compounds effective at treating autoimmune or infectious diseases." Office Action, p. 9, 11. Since claim 111 is a product claim that is not limited by an intended use or effect, enablement does not require support for all cancers or diseases. Rather, an enabled disclosure of *any* use is sufficient to preclude a rejection of claim 111 for non-enablement. *See* M.P.E.P. § 2164.01(c). Thus, the absence of data showing activity against all types of cancer or autoimmune and infectious diseases does not support the non-enablement of claim 111.

Applicants respectfully submit that the guidance provided throughout the specification and the high degree of skill in the pharmaceutical art are sufficient to enable the compositions of claim 111. Accordingly, applicants respectfully request that the rejection of claim 111 for lack of enablement be withdrawn.

V. THE CLAIMS ARE PATENTABLE UNDER 35 U.S.C. § 112 SECOND PARAGRAPH

Claims 1, 2, 7, 17-21, 27, 111-121 and 123 stand rejected under 35 U. S.C. § 112, second paragraph, for allegedly omitting essential elements. In particular, it is asserted that "the connectivity between R^4 and R^5 and the backbone when R^4 and R^5 join and the connectivity between $(CR^aR^b)_n$ and the formula when R^4 and R^5 join" are missing, and that

such omission amounts to a gap between the elements. Office Action, p. 11. Applicants respectfully disagree. However, without acquiescing to the rejection and solely to expedite prosecution of the instant case, applicants have herein amended independent claims 1, 7, and 44 by rearranging the placement of the phrase "form a ring with the carbon atom to which they are attached". Applicants respectfully request withdrawal of the rejections under § 112, second paragraph.

VI. THE CLAIMS ARE PATENTABLE UNDER 35 U.S.C. § 102(e)

Claims 1, 2, 7, 9, 17-21, 27, 54, 63, 66, 79, 111, 120, 121 and 123 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Publication No. 20050123536 to Law et al.. In particular, it is alleged that example 5 of the Law *et al.* publication teaches the compound of instant claim 79, wherein p is 8 and L is an anti-CD30 monoclonal antibody. Applicants respectfully traverse.

U.S. Application No. 10/496,628, which published as U.S. Pub. No. 20050123536, is a U.S. National Stage Application of International Application No. PCT/US02/37223, filed November 20, 2002, which claims priority to U.S. Provisional App. No. 60/331,750, filed Nov. 20, 2001. Example 5 of U.S. Pub. No. 20050123536 and related subject matter is not disclosed in the earliest priority application (Provisional App. No. 60/331,750). Thus, the effective priority date of the present application (based on Provisional App. No. 60/400,403, filed July 31, 2002) antedates the allegedly anticipatory subject matter. Applicants therefore respectfully request withdrawal of the rejections under 35 U.S.C. § 102(e).

VI. DOUBLE PATENTING

Claims 1, 2, 7, 9, 17-21, 27, 54, 63, 66, 79, 111, 120 and 121 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over:

claims 1-44 and 48-103 of copending U.S. App. No. 11/833,954,
claims 1-36 and 40-89 of copending U.S. App. No. 11/833,959,
claim 11 of copending U.S. App. No. 12/016,978,
claims 74-94, 109 and 222-235 of copending U.S. App. No. 10/983,340,

claims 1-18 of copending U.S. App. No. 11/667,437,

claims 53-99 of copending U.S. App. No. 11/994,459, and

claims 28-73 of copending U.S. App. No. 11/994,809.

Claims 112, 113 and 116 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over:

claims 1-54 of copending U.S. App. No. 11/833,961,

claims 1-54 of copending U.S. App. No. 11/833,964,

claims 8 and 9 of copending U.S. App. No. 10/558,811, and

claims 1-40 of copending U.S. App. No. 11/667,029.

Claims 111-119 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over:

claims 100-134 of copending U.S. App. No. 11/994,459, and

claims 74-109 of copending U.S. App. No. 11/994,809.

Claims 111-114, 116, 117 and 119 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over:

claims 19-30 of copending U.S. App. No. 11/667,437.

Applicants disagree with the examiner's characterization of certain references as anticipatory and the characterization of certain claims as subgeneric to claims of the instant application. In addition, Applicants note that a Notice of Allowance has recently been issued for U.S. App. No. 10/983,340. However, without addressing the propriety of the rejections, and specifically the examiner's interpretation of what the cited references teach or suggest, applicants respectfully request that the rejections be deferred until there is allowable subject matter in the present application. Applicants will consider filing terminal disclaimer(s) at that time if warranted by the rejections in view of the allowed claims.

VII. CONCLUSION

In view of the foregoing, the application is now in condition for allowance. The prompt issuance of a formal Notice of Allowance is therefore requested.

If the examiner believes a telephone conference would expedite allowance of this application, please telephone the undersigned at 206-389-4558.

Date: July 29, 2008

/Robert J. Yamasaki/

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